Drug-Induced Liver Injury (DILI) including Acetaminophen (APAP) 2014: Practical Tips

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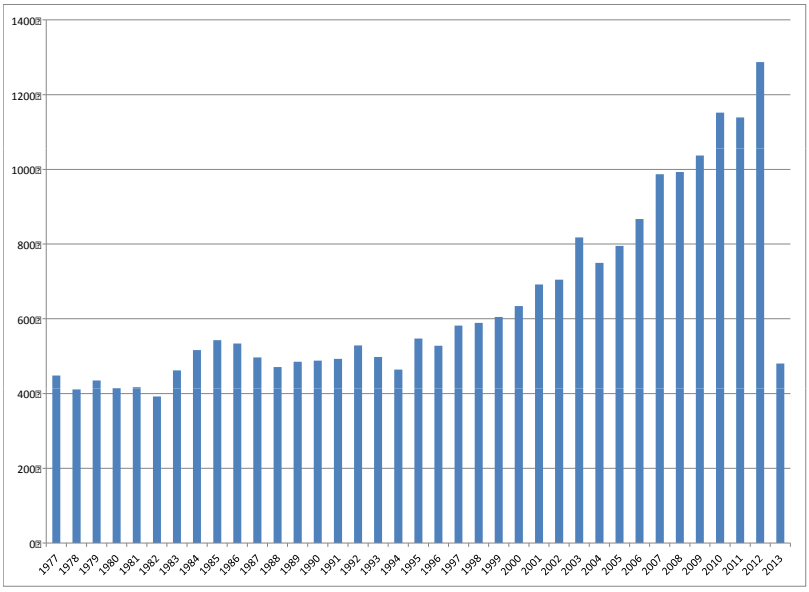
DILI 2014: Aims/Topics

Aim: Discuss Clinical Trends in DILI and Acetaminophen Liver Injury

Topics:

- **Overall scope of the problem**
- **Problems in diagnosis**
- **Issues regarding causality**
- **Acetaminophen clinical tips**
- **Treatment of DILI/APAP**

Number of DILI Articles Published Annually, currently >1200



Etiology of Acute Liver Failure in the USA

Adult Registry (n = 2,000)

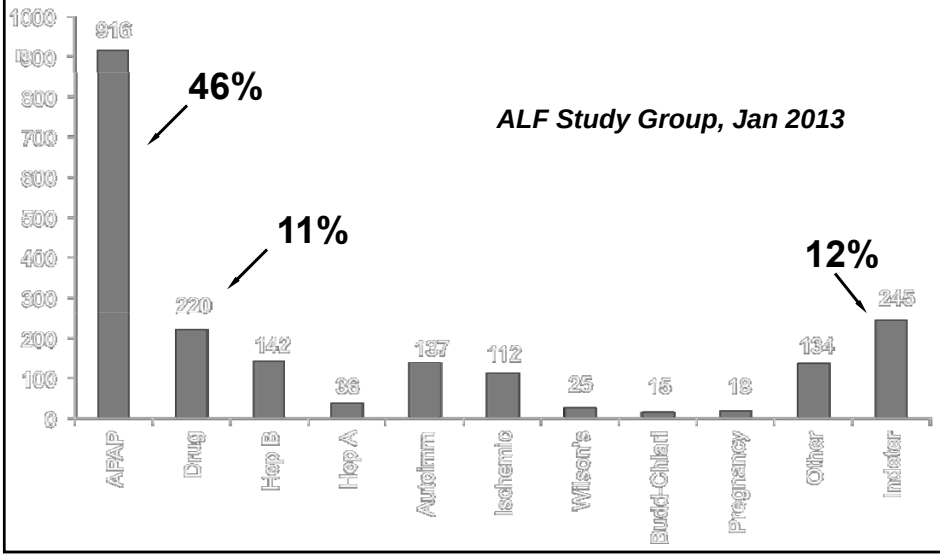


Table 1 | **Regulatory actions due to non-allergic hepatotoxicity***

Drug	Use	Regulatory action
Bromfenac	Analgesic	Withdrawn
Troglitazone	Diabetes	Withdrawn
Felbamate	Anticonvulsant	Restricted use
Pemoline	CNS stimulant	Restricted use
Tolcapone	Parkinson's disease	Restricted use
Trovafloxacin	Antibiotic	Restricted use
Acetaminophen	Analgesic	Warnings
Leflunomide	Immunomodulator	Warnings
Nefazodone	Antipsychotic	Warnings
Nevirapine	Antiviral (HIV)	Warnings
Pyrazinamide	Antituberculosis	Warnings
Rifampin	Antituberculosis	Warnings
Terbinafine	Antifungal	Warnings
Valproic acid	Anticonvulsant	Warnings
Zafirlukast	Asthma	Warnings

Ximelagatran **Anticoagulant** **Not approved (2006)**

Telithromycin **Antibiotic** **Restricted Use (2007)**

Adapted from: ***Kaplowitz, Nat Rev Drug Disc 2005***

The Conundrum of Idiosyncrasy: Why are just a few patients susceptible?

"idio-sug-krasia" (Hippocrates, ~ 400 B.C.)

- **idios (ιδιος) - one's own, self**
- **syn (συν) - together**
- **crasis (κρασις) - mixing, mixture**

a person's own individual mixture of characteristics, factors; uniqueness

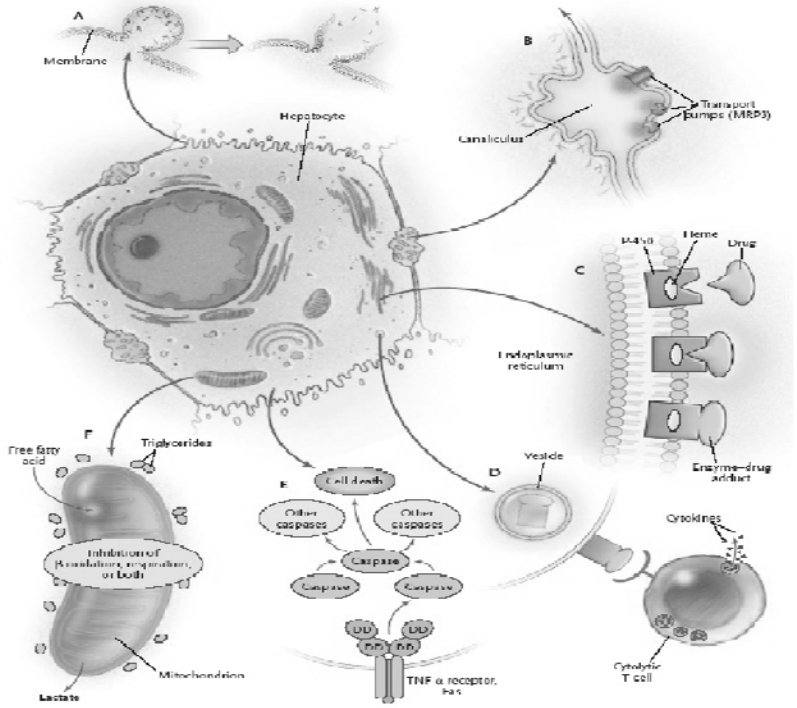
It does NOT mean rare, unexpected, unexplained, although it may or may not be any or all of them!

Features of Idiosyncratic Drug Reactions

1. Occur rarely, not really dose related
2. Similar consistent pattern for each drug
3. Similar drugs exhibit similar features, "class effects"
4. Individual drugs in a class still vary considerably
5. Reactions occur at varying time intervals after ingestion (3 days to one year)

Features of Idiosyncratic Drug Reactions

6. Reactions vary in severity, but typically severe and fatal if drug continued
7. Mild injury often disappears with continued use (adaptation)
8. Rarity of most reactions suggests multiple hits
9. Re-challenge is virtually always met with greater severity, shorter latency
10. Most drugs causing idiosyncrasy are at doses >100 mg/day



-From: ***Lee, NEJM 2003***

Mitochondrial injury: HIV drugs, valproate, others

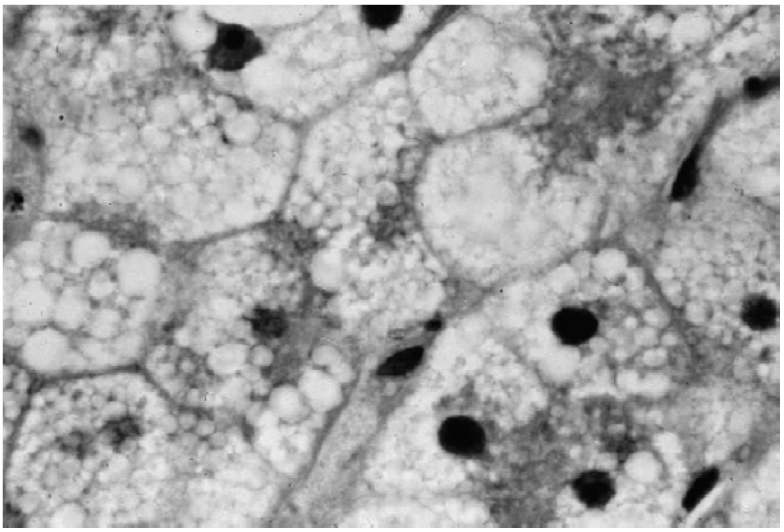


Image is courtesy Jay Lefkowitch, Columbia University

Drugs causing cholestasis

- More than one case report:
  Amoxicilliin/clavulanate
  Carbamazepine
  Erythromycin esters
  Flucloxacillin
  Methyltestosterone
  Phenytoin
  Prochlorperazine
  Trimethoprim/sulfa
- Less frequent:
  Azathioprine
  Barbiturates
  Captopril
  Allupurinol
  Clindamycin

Black cohosh hepatotoxicity: autoimmune hepatitis

35 yo woman, began a mail order pill one/day.

Admitted 4 wks later with coma.

TB 19.3, AST 835/ALT 674, INR 3.9, ANA 1:640.

Transplantation required.

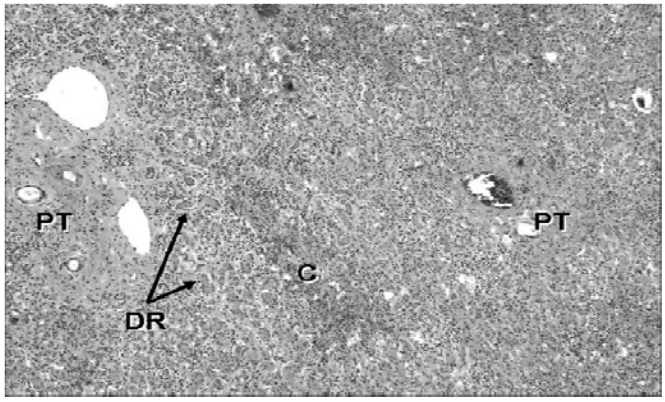
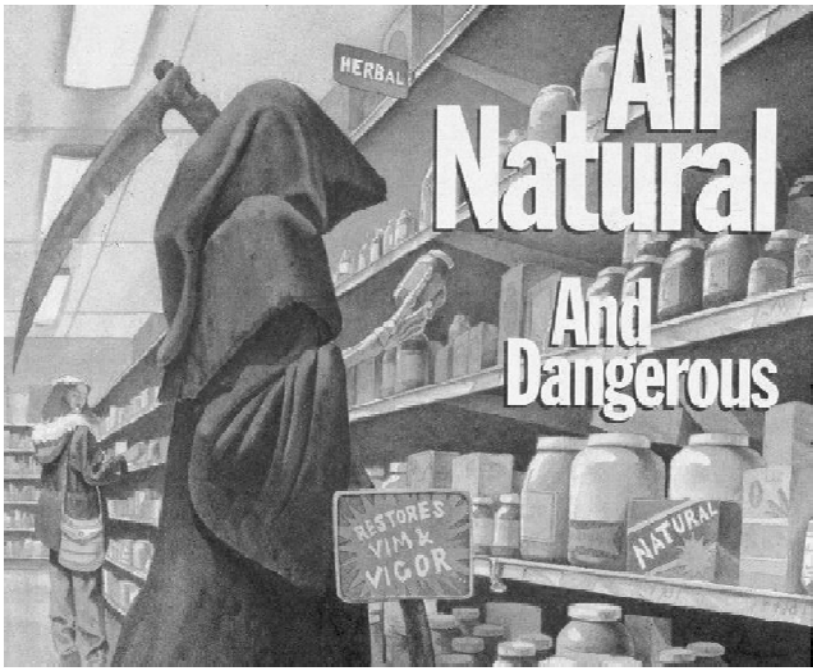
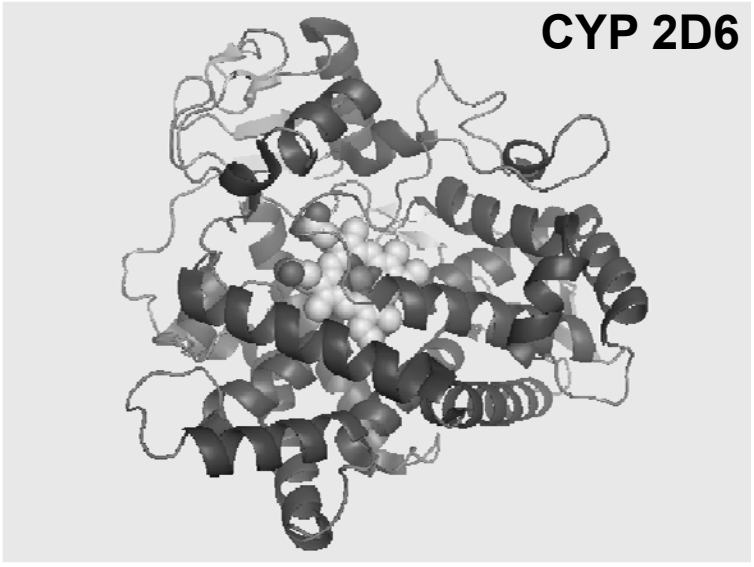


Image is courtesy Jay Lefkowitch, Columbia University



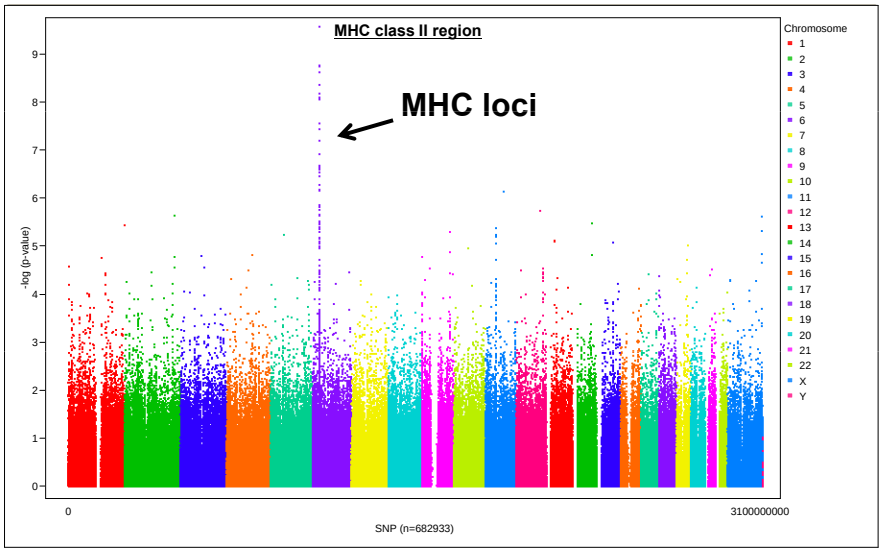
New York Review of Books, 2003



Author: BorisTM

Genome-wide Association Results for All SNPs

p-values Plotted by Genomic Location; >5xULN ALT/AST



Singer JB, Lewitzky S, Leroy E, et al. A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury. Nature Genetics 2010; 42:711-14

Genomics will help solve the riddle of idiosyncrasy

Techniques will vary from directed SNP analyses to GWAS

There may be relatively few 'susceptibility MHC haplotypes'

Still, much complexity will likely remain:

Initial susceptibility: MHC haplotype PLUS

Downstream modulation (e.g., IL-10 genes)

Table 4. Haplotypes strongly associated with specific drug-related diseases

HLA-B*1502	Stevens Johnson/TEN	carbamazepine
DRB1*0701/DQA1*02	Hepatotoxicity	ximelagatran
DRB1*1501-DQA1*0102-DQB1*0602-DRB5*0101	Mixed hepatotoxicity	amoxicillin/clavulanate
HLA-B*5701	Hypersensitivity/hepatotoxicity	abacavir
HLA DRB1*0701 and HLA B*5701	Hepatotoxicity	flucloxacillin
DRB1*1302 and DQB1*0604	Hepatotoxicity	ticlopidine
DQA1*0102	Hepatotoxicity	lumiracoxib

Causality Assessment

- How do we know a drug has caused the injury?
- Answer: Guilt by association
- RUCAM, a rudimentary tool for determining causality
- Better systems are needed!

Components of RUCAM (Roussel Uclaf Causality Assessment Method)

Points awarded for the following categories:

1. Time to onset
2. Course, "dechallenge"
3. Risk factors (age, alcohol, pregnancy)
4. Concomitant drugs
5. Search for non-drug causes
6. Previous information on hepatotoxicity of the drug
7. Response to re-administration

Problems: too little data, inter/intra-observer variation, Inclusion of non-valid parameters

Basic Steps in Causality

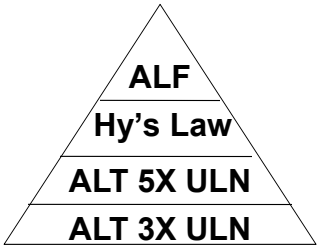
Most injury is to hepatocytes: determine <u>is it 'hepatitis?'</u>

- **Measure aminotransferases and are they new?**
- **Assess severity: level of ALT, INR, encephalopathy**
- **What are other possible causes? Alcohol, Viral, Ischemia, (gall)Stones = "AVIS."**
- **What (other) drugs are being taken?**
- **What is likelihood of each drug?**

Hyman Zimmerman, MD 1914-1999

The spectrum of severity (suspect drugs provide 'signals')

- Percent with ALT elevations higher than comparators: 3X ULN, 5X ULN, 10X ULN
- Occurrence of Hy's Law cases (jaundice)
- Occurrence of acute liver failure



DILIN: US NIH-sponsored network 2003-2018

https://dilin.dcri.duke.edu/

DILIN Causality (Likelihood) Score, given by percent

1 = **Definite: >95% Liver injury is typical for the drug or herbal product ('signature' or pattern of injury, timing of onset, recovery). The evidence for causality is 'beyond a reasonable doubt'**

2 = **Highly likely: 75–95% The evidence for causality is 'clear and convincing' but not definite**

3 = **Probable: 50–74% The causality is supported by 'the preponderance of evidence' as implicating the drug but the evidence cannot be considered definite/highly likely.**

4 = **Possible: 25–49% The causality is not supported by 'the preponderance of evidence'; however, one cannot definitively exclude the possibility**

5 = **Unlikely: <25% The evidence for causality is 'highly unlikely' based upon the available information**

6 = **Insufficient data**

Problems with RUCAM and DILIN Expert Opinion

RUCAM

1. **Full data rarely available**
2. **Dechallenge often cannot be determined**
3. **Risk factors (age, alcohol) unwarranted**
4. **Good people still get different scores!**

Bottom line: Lacks accuracy!

DILIN

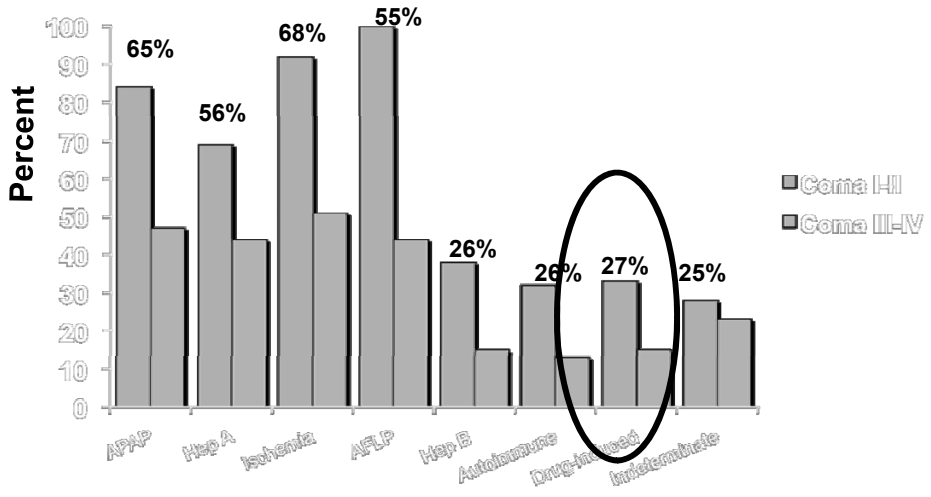
1. **Expert opinion requires 'experts'!**
2. **Impractical/takes time**
3. **Has better data /good inter-observer consistency**
4. **Is useful for establishing phenotype for genetics**

Bottom line: Lacks day to day clinical utility!

Most frequent DILI agents in adults

	ALFSG	DILIN
Antibiotics	N=137	N=519
INH (w/wo rif/pyraz)	25	28
Sulfa (TMP/SMX, sulfasalazine	12	8
Nitrofurantoin	11	23
Azoles	6	12
Amox/Clavulanate	0	37
Others	13	115
Anti-convulsants		
Phenytoin	8	7
Others including psychotropics	10	43
NSAIDS	7	21
Herbs	14	59

Transplant-free survival by etiology and coma grade



Coma grade I-II patients had ~50% better survival than III-IV

Review: Key Steps in DILI

Call it hepatitis (or some other form)

Look HARD for the specific drugs

Make sure the temporal relationship fits

Rule out 'AVIS'

Think about specific drug patterns and consult livertox.nih.gov

Think like an expert!

Summary of this talk; additional points

- **Causality assessment is a black art, not a science**
- **Think outside your comfort zone of hepatocellular injury—it is not all INH and TMP/SMX!**

Other disease patterns for the future

- **Vanishing bile ducts due to antibiotics**
- **Vascular injury yielding nodular regenerative hyperplasia**
- **Autoimmune hepatitis due to biologics**
- **Congestive heart failure due to chemotherapy**

Best advice

Use livertox.nih.gov as your source for good info

Acetaminophen (Paracetamol) Hepatotoxicity

- Dose-related toxin
- Popular (mild) pain reliever
- Dwarfs all other forms of acute liver injury
- Largest selling OTC product/largest Rx generic
- Multi-billion dollar product/well-protected brand
- >100,000 calls annually to poison control centers
- 400+ deaths annually in the US, similar in EU
- Iconic model for studying liver injury
- Keeps basic scientists and clinicians employed!

Historical highlights I: Recognizing APAP problem

- 1960's Acetaminophen (paracetamol) first used in UK
- 1966: First reports of hepatotoxicity
- 1970's Becomes common analgesic/suicide agent in UK
- 1973 Mitchell and Jollow outline mechanism of injury
- 1975 Rumack develops nomogram to predict toxicity
- 1977 First report of NAC to prevent/manage toxicity
- 1986 Seeff and Zimmerman: association with alcohol--'Therapeutic misadventure' described in US

Ann Int Med 1986

CLINICAL REVIEW

Acetaminophen Hepatotoxicity in Alcoholics

A Therapeutic Misadventure

LEONARD B. SEEFF, M.D.; BRENDA A. CUCCHERINI, M.P.H.; HYMAN J. ZIMMERMAN, M.D.; EDWARD ADLER, M.D.; and STANLEY B. BENJAMIN, M.D.; Washington, D.C.; and Louisville, Kentucky

We have treated 6 chronic alcoholics and identified an additional 19 reported in the literature who developed severe hepatotoxicity from acetaminophen taken in apparently moderate doses. The clinical disease in these 25 patients had a characteristic pattern: mild to moderate jaundice; mild to severe coagulopathy; and strikingly abnormal aminotransferase levels, values inconsistent with either acute alcoholic hepatitis or viral hepatitis. The possible causes for the injury from ostensibly nontoxic drug levels appear to be either the induction by chronic alcohol intake of the cytochrome P-450 system responsible for converting acetaminophen to a toxic metabolite, or the effect of alcoholism and the associated malnutrition in reducing the glutathione concentration, responsible normally for preventing hepatotoxicity by conjugation with the toxic metabolite. The research data pertaining to the apparent enhanced toxicity from chronic alcoholism are reviewed. Despite the low frequency of ethanol-potentiated acetaminophen hepatotoxicity, alcoholics should be cautioned about the use of

headaches. He was admitted to the hospital with the following laboratory values: aspartate aminotransferase (AST), 19 710 IU/L; alanine aminotransferase (ALT), 4560 IU/L; serum bilirubin, 13.0 mg/dL; prothrombin time, 12 seconds longer than the control; and a negative test for hepatitis B surface antigen (HBsAg). His hospital course included the development of disseminated intravascular coagulopathy, hemolysis, and ascites, all of which resolved with time. The patient recovered and was discharged without unusual sequelae.

PATIENT 2

A 30-year-old male chronic alcoholic with a painful apical tooth absess had, over 3 days, ingested 12.5 g of acetaminophen together with a six-pack of beer each day. He was admitted to the hospital because his laboratory values included a bilirubin level of 2.4 mg/dL; AST, greater than 10 000 IU/L; lactic dehydrogenase level, 4980 IU/L; and prothrombin time, 5.4 seconds above the control. Other values included blood urea nitrogen, 9 mg/dL; creatinine, 1.1 mg/dL; amylase, 40 U/dL; hematocrit, 52; and a leukocyte count of 8900/mm^3 with a shift to the left. Serologic tests for hepatitis B were negative. The

The New England Journal of Medicine

ACETAMINOPHEN TOXICITY IN AN URBAN COUNTY HOSPITAL

FRANK V. SCHIØDT, M.D., FEDJA A. ROCHLING, M.D., DONNA L. CASEY, B.S., AND WILLIAM M. LEE, M.D.

ABSTRACT

Background The prevalence and characteristics of acetaminophen-associated liver injury in hospitalized patients are not well defined.

Methods We identified patients hospitalized for excessive acetaminophen ingestion at an urban county hospital over a 40-month period (1992 to 1995) and reviewed their medical records to determine the incidence and clinical features of the ingestions and their outcomes.

Results Of the 71 patients studied, 50 were classified as having taken acetaminophen during suicide attempts and 21 as having accidentally poisoned themselves while attempting to relieve pain. The suicidal patients had ingested almost twice as much acetaminophen as those in the accidental-overdose group (median, 20 vs. 12 g; P = 0.009). Among the patients for whom data were available, 63 percent of those in the accidental-overdose group and 25 percent of those in the suicidal group were chronic alcohol abusers (P = 0.009). The patients in the accidental-overdose group more often had severe liver necrosis (aminotransferase levels, >3500 IU per liter; 52 percent vs. 14 percent; P = 0.002) and were more likely to have hepatic coma (33 percent vs. 6 percent, P = 0.006). There were four deaths (19 percent) in the accidental-overdose group and one (2 percent) in the suicidal group (P = 0.04). Five patients — three in the accidental-overdose group and two in the suicidal group — had ingested 4 g of acetaminophen or less. Acetaminophen ingestion accounted for 12 percent of all patients hospitalized with overdoses (71 of 589) and 40 percent of patients with acute liver failure (10 of 25) during the study period.

Conclusions In an urban county hospital, patients

the most common cause of acute liver failure in the United Kingdom. A second pattern, apparently more prevalent in the United States, is observed in alcoholic or fasting patients who ingest smaller amounts of acetaminophen only to relieve pain and in whom alcohol use or starvation appears to worsen the liver injury.[1,5-7] Suicidal overdoses have been common in the United Kingdom since the 1970s,[8] and their incidence appears to be increasing in the United States.[9,10] Despite these reports, little information is available on the overall incidence and severity of acetaminophen hepatotoxicity in the United States.

We retrospectively examined the records of patients with acetaminophen toxicity in an urban county hospital over a 40-month period to determine the incidence and clinical profile of acetaminophen-associated liver injury.

METHODS

The study group consisted of all patients admitted to Parkland Memorial Hospital, the sole public hospital in Dallas County, Texas (with approximately 40,000 admissions annually), for potential or actual acetaminophen hepatotoxicity between January 1, 1992, and April 30, 1995. Since the hospital does not perform liver transplantation, no patients were referred for that purpose, and no patients required transplantation.

The patients' medical records were identified and retrieved in two ways. First, we used coding software (Code 3 N coder, 3M, Minneapolis) to search the data base for all patients coded as having hepatic necrosis (a category that included acute liver failure), drug overdose, or alcoholic hepatitis. Patients defined clinically as having typical alcoholic hepatitis were excluded from further study.[11] Second, we reviewed the records of all patients in whom acetaminophen levels greater than 10 mg per liter were measured. We confirmed that a patient had had substantial acetaminophen

Parkland Hospital study of APAP overdoses

Suicidal: n=50	Unintentional: n=21
• Suicide admitted	• Suicide denied
• Single time point	• Several days' use
• No cause of pain	• Reason for pain
• Early presentation	• Late presentation
• 20% ALT > 1,000	• Virtually all high ALT
• 1 ALF/death in 50 (2%)	• 8 ALF; 6 (29%) died

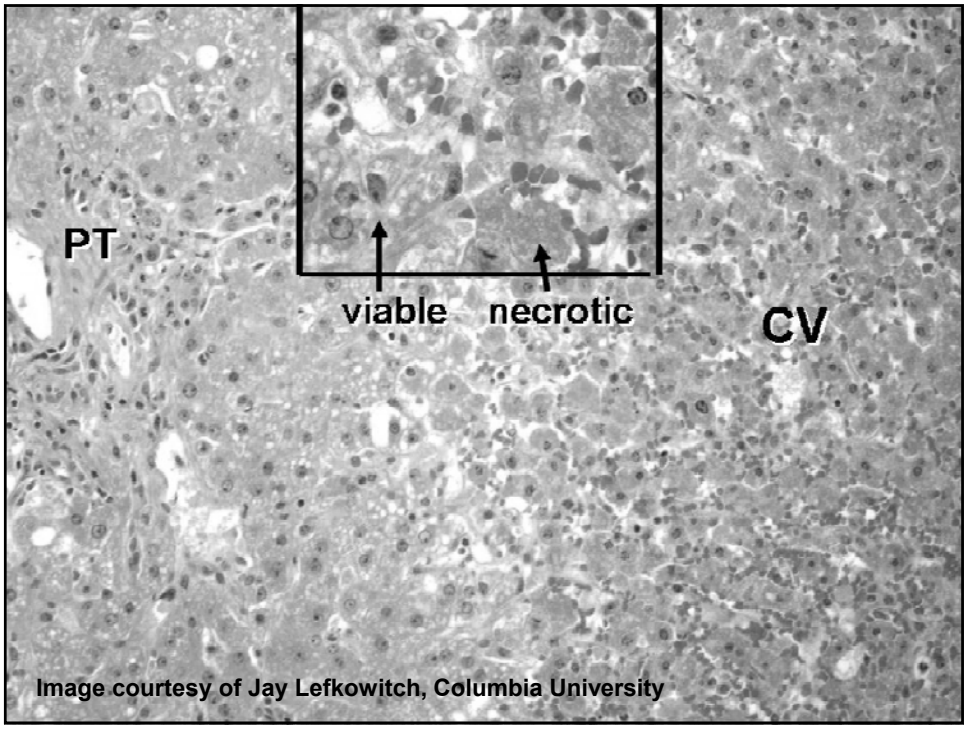
Schiødt et al., NEJM 1997:337:1112-17

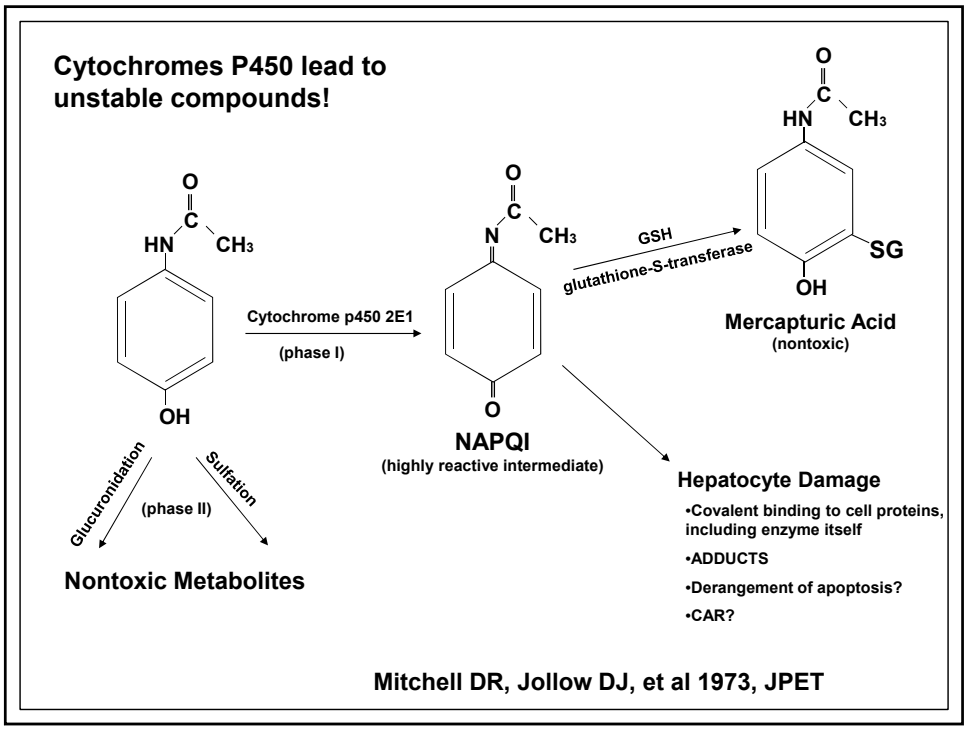
Only 9 of 71 had ALF, but they were mostly unintentional

Acute Liver Failure Study Group: based at UTSW
Rationale: Network to study a rare disease

- Began in 1998, 15 adult, 10 pediatric sites
- 2,300 cases in adult, ~1,100 in pediatric registry
- New added definition: ALI—INR > 2.0/no enceph
- Three directions:
  - Prospective clinical data, sera, plasma, DNA, tissue
  - Numerous ancillary studies in progress
  - Therapy trials: NAC trial done, STOP-ALF in progress

Funding: NIDDK U-01 through 2015


PT
viable
necrotic
CV
Image courtesy of Jay Lefkowitch, Columbia University


Cytochromes P450 lead to unstable compounds!
HN
CH3
OH
Cytochrome p450 2E1
(phase I)
N
NAPQI
(highly reactive intermediate)
GSH
glutathione-S-transferase
SG
Mercapturic Acid
(nontoxic)
Glucuronidation
Sulfation
(phase II)
Nontoxic Metabolites
Hepatocyte Damage
•Covalent binding to cell proteins, including enzyme itself
•ADDUCTS
•Derangement of apoptosis?
•CAR?
Mitchell DR, Jollow DJ, et al 1973, JPET

Comparison of Different ALF Etiology Groups

N = 2000

	APAP N=916	Drug n=220	Indeterminate n=245	HepA/HepB n=36/142	All Others N=441
Age (median)	37	46	39	49/43	45
Sex (% F)	76	69	59	44/44	71
Jaundice to coma (Days)	1	11.5	11	4/8	7
Coma ≥3 (%)	53	35	48	56/52	38
ALT (median IU)	3773	639.5	865	2275/1649	681
Bili (median)	4.3	19.8	21.1	12.3/18.4	13.9
Tx (%)	9	40	42	33/39	32
Spontaneous Survival (%)	66	24	22	50/21	31
Overall Survival (%)	73	58	60	72/55	58

Treatment for APAP Overdose

N-acetylcysteine (NAC) is an effective antidote!

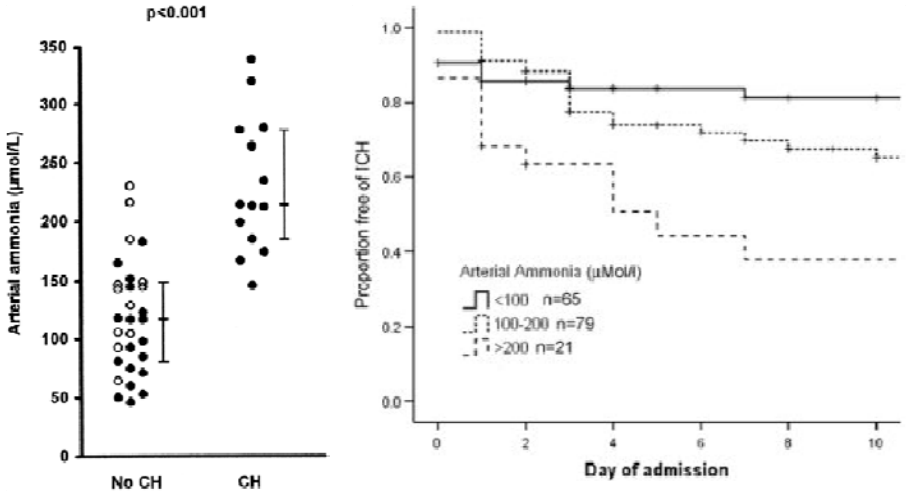
- IV NAC will totally prevent toxicity if given < 12 hrs
- Uncertain benefit after 30 hours
- Supportive care in ICU: may develop fatal complications: brain edema.
- Initial evaluation: is it ALF? If so, is he/she a LT candidate? If so, consider early transfer to liver transplant center.

Ornithine Phenyl Acetate: STOP-ALF Trial

Lower ammonia to manage cerebral edema

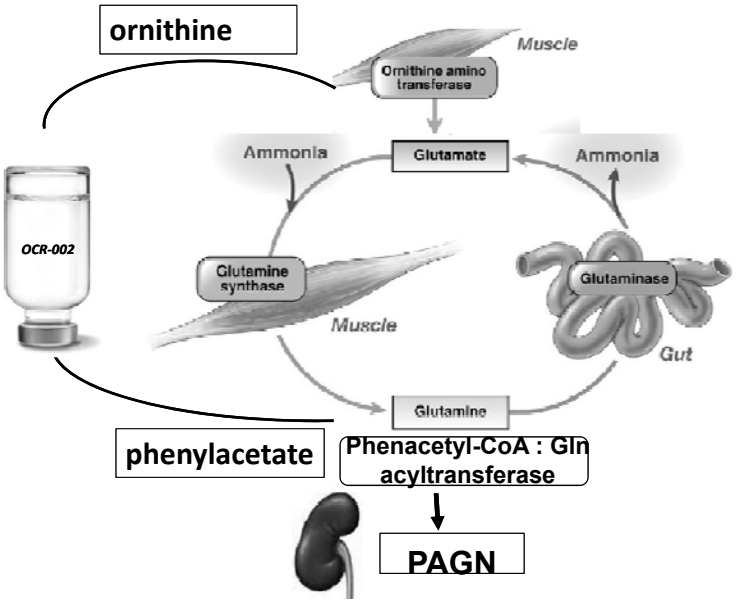
- Ammonia is the putative cause for cerebral edema
- OPA traps ammonia and allows renal excretion
- Could be used prophylactically or as treatment
- IV, few side effects, might work in cirrhosis also
- ALFSG is studying the acetaminophen ALF/ALI group since July 2012—to be completed 2014.

Several studies highlight role of NH_3 in raising ICP

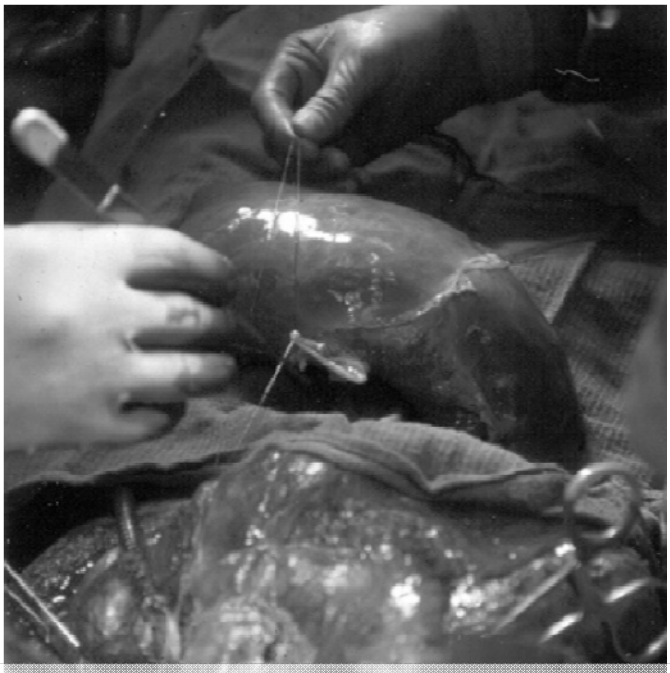


Clemmesen J et al Hepatology 1999.

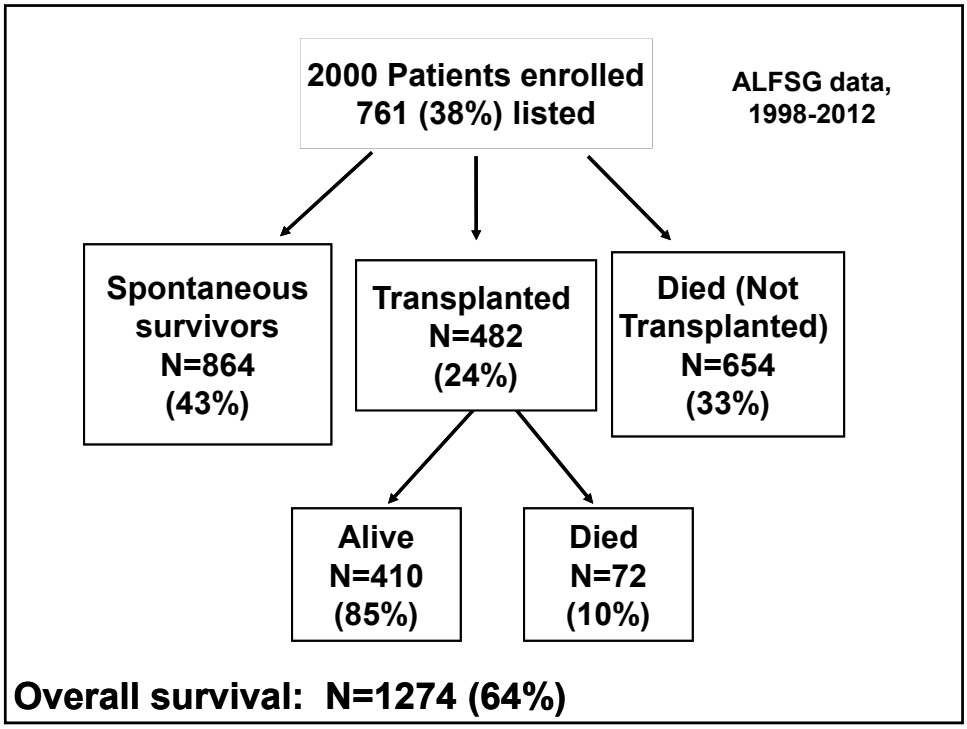
OCR-002 Uses Physiological Pathways to Eliminate Nitrogen

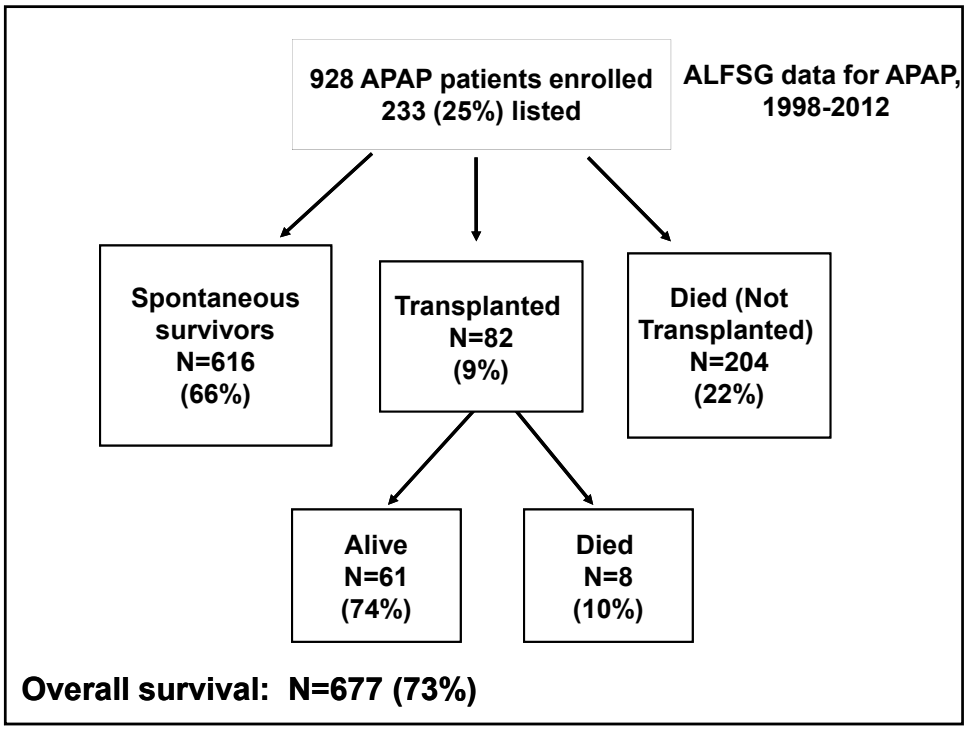


Lee WM, Jalan RV. Gastroenterology 2009



Goran Klintmalm, Baylor University Med Ctr, Dallas


2000 Patients enrolled
761 (38%) listed
ALFSG data,
1998-2012
Spontaneous survivors N=864 (43%)
Transplanted N=482 (24%)
Died (Not Transplanted) N=654 (33%)
Alive N=410 (85%)
Died N=72 (10%)
Overall survival: N=1274 (64%)


928 APAP patients enrolled
233 (25%) listed
ALFSG data for APAP,
1998-2012
Spontaneous survivors N=616 (66%)
Transplanted N=82 (9%)
Died (Not Transplanted) N=204 (22%)
Alive N=61 (74%)
Died N=8 (10%)
Overall survival: N=677 (73%)

APAP Hepatotoxicity: Summary

- Still an important problem dwarfing DILI!
- Opioid compounds involved in 40+%
- Comprises 18% of indeterminate ALF
- Frequent psych issues and drug abuse in both groups
- Multiple products important in at least 20%, more in pain patients.
- Renal injury is common in APAP
- Still the largest cause of death from ALF in US

Overall Summary: DILI and APAP 2014

- Identifying drug-induced hepatotoxicity is vital
- Bad outcomes can and do occur
- Key here is taking a great history
- Loyal patients sometimes hurt themselves
- Be aware of agents that cause toxicity and alert to new ones. Use Livertox.nih.gov to look things up
- OSU is a good source for information and consultation: we specialize in handling patients with Acute Liver Failure!!